BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. II.*

AMINES OF 8-CHLORO-2,3,4,5-TETRAHYDRO-1-BENZOXEPIN SERIES**

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8-Chloro-2,3-dihydro-4*H*-1-benzoxepin-5-one (*I*) was transformed to oxime *VIII*, secondary alcohol *XII*, chloride *XIV*, formamido derivative *XVI*, tertiary alcohols *XXXIII* and *XXXVI* and the Mannich base *XXXIX*. These products were further transformed by simple reactions to the required amines. In the course of the work, several more complicated by-products were isolated and their structures were proposed (*XXIX*, *XXXI*, *XLIII*). Some of the prepared amines displayed a hypotensive effect (*XVII*, *XVIII*, *XXI*, *XXII*, *XXXIII*), compound *XX* showed antireserpine activity and inhibited monoamine oxidase, compound *XXXIII* had an antiinflammatory activity. Several other compounds showed indications of hypoglycaemic, spasmolytic, local anaesthetic, adrenolytic, analgesic and diuretic activities.

1-Benzoxepin and its derivatives partially saturated in the seven-membered ring which may be regarded as homologues of benzofuran and chroman, and des-benzo analogues of dibenz(*b*,*e*)oxepin and dibenz[*b*,*f*]oxepin, represent pharmaceutically promising systems, their amines potentially possessing different types of neurotropic and cardiovascular activity. Particularly suitable intermediates of the synthesis of such amines are 2,3-dihydro-4*H*-1-benzoxepin-5-one and its Ar-substitution derivatives, the synthesis and basic chemistry of which has been studied since 1931 by several teams[1-4]. With the objective of discovering new drugs, Zaugg and coworkers studied this group systematically[5-10]. They investigated compounds that were not substituted in the benzene ring; they prepared especially 5-phenyl-5-amino-2,3,4,5-tetrahydro-1-benzoxepin[5,6], its 5-(4-methylpiperazino) analogue[7], 5-phenyl-5-aminomethyl-2,3,4,5-tetrahydro-1-benzoxepin and its N-substitution derivatives[8] and, finally, the aminoalkyl esters and aminoalkyl thioesters of 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylic acid[9,10] which were reported to possess analgesic, spasmolytic, local anaesthetic and hypotensive effects. De Stevens[11] described the synthesis of 4-dimethylaminomethyl-5-phenyl-5-propionoxy-2,3,4,5-tetrahydro-1-benzoxepin as a compound with analgesic effects. Finally Arnold and coworkers [12] patented a number of the corresponding 5,4′-spirohydantoins (including compounds substituted in the benzene ring) which were reported to act as anticonvulsants.

In the present study where we proceeded somewhat in parallel to our work in the group of derivatives of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[13] and 2,3,4,5-

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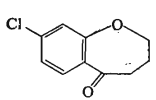
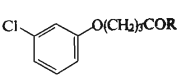
** Dedicated to Professor Dr M. Pailer on the occasion of his 60th birthday.

tetrahydro-1-benzothiepin[14], we also used the "ketone approach", using 8-chloro-2,3-dihydro-4*H*-1-benzoxepin-5-one (*I*) as the principal compound of the whole preparation. This ketone was apparently an intermediate in the preparation of one of Arnold's products[12] but its preparation was not described in the corresponding patent. We obtained it in a high yield by cyclization of 4-(3-chlorophenoxy)butyric acid (*II*) with the aid of polyphosphoric acid (method in ref.[2,15]). The preparation of *II* was achieved by acid-forming cleavage of the alkylation product of ethyl acetoacetate with 2-(3-chlorophenoxy)ethyl *p*-toluenesulfonate[16]. For the same purpose we used now successfully the reaction of *m*-chlorophenol[17,18] with γ-butyrolactone (method in ref.[19]). The acid *II* was converted in the usual way to the ethyl ester *III* and the chloride *IV*. From the chloride, we prepared the amide *V*, the diethylamide *VI* and the 2-diethylaminoethylamide *VII*.



I

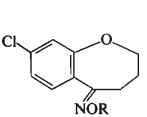


II, R = OH
III, R = OC_2H_5
IV, R = Cl

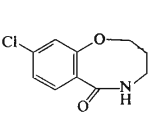
V, R = NH_2
VI, R = $N(C_2H_5)_2$
VII, R = $NH(CH_2)_2N(C_2H_5)_2$

The conventionally prepared oxime *VIII* was alkylated with sodium ethoxide and 2-dimethylaminoethyl chloride; the product apparently has the structure of the O-alkyl derivative *IX* [ν(C=N) 1620 cm^{-1}]. Beckmann's rearrangement of oxime *VIII* by treatment with phosphorus pentachloride in a mixture of ether and benzene yielded a small amount of the lactam $C_{10}H_{10}ClNO_2$ for which the constitution of the 1,5-oxazocine derivative *X* is preferred on the basis of its IR spectrum [ν(Ar. .CONH) 1670 cm^{-1}]. In an attempt at a reaction of ketone *I* with sodium azide[20] in sulfuric acid we obtained the tetrazole derivative as the single product, its structure being apparently that of *XI*.

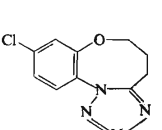
Reduction of ketone *I* with sodium borohydride results readily in 8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XII*) which reacts with sodium amide and 2-dimethylaminoethyl chloride to ether *XIII*. When treating alcohol *XII* with anhydrous hydro-



VIII, R = H
IX, R = $(CH_2)_2N(CH_3)_2$



X

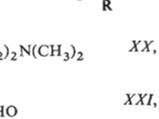


XI

gen chloride an oily chloro derivative *XIV* is formed but it could not be prepared in analytically pure form. For further reactions it was used in the crude state. During attempts at distillation it is decomposed, a minor product formed being 8-chloro-2,3-dihydro-1-benzoxepin (*XXV*) arising through elimination of hydrogen chloride. The major product is a high-boiling yellow liquid which is a dimer of *XXV* (confirmed by mass spectrum); according to its NMR spectrum it is most likely *XXIX*.

When attempting to reduce the oxime *VIII* with sodium and ethanol a simultaneous hydrogenolysis takes place giving a chlorine-free amine *XXX*. Hence another method had to be used for the preparation of amine *XV*. Rather suitable appeared to be Leuckart's reaction of ketone *I* with formamide and with formic acid which gives rise to a high yield of the formamido derivative *XVI*. Its hydrolysis in boiling hydrochloric acid gives rise to the hydrochloride of the primary amine *XV* while reduction with lithium aluminium hydride yields the methylamino derivative *XVII*. The dimethylamino derivative *XVIII* was prepared from the primary amine *XV* by methylation with formaldehyde and formic acid, and tertiary amines *XIX* and *XX* were obtained by alkylation of the secondary amine *XVII* with allyl bromide or propargyl bromide. Reaction of amine *XV* with S-methylisothiuronium sulfate in boiling water gave rise directly to the hemisulfate of 5-guanidino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXI*).

Substitution reaction of the crude chloro derivative *XIV* with 1-methylpiperazine and 1-phenylpiperazine[21] produced low yields of the piperazino derivatives *XXII* and *XXIII*. Elimination to the olefinic derivative *XXV* predominates. In the reaction with methylpiperazine about 10% of another compound was obtained in one experiment, the analysis and mass spectrum of which suggested that the molecule is built from two chlorobenzoxepin fragments and one methylpiperazine fragment. We assume that the compound was formed through an analogy of Michael's addition

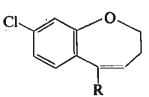


XII, R = OH
XIII, R = $O(CH_2)_2N(CH_3)_2$
XIV, R = Cl
XV, R = NH_2
XVI, R = NHCHO
XVII, R = $NHCH_3$
XVIII, R = $N(CH_3)_2$
XIX, R = $N(CH_3)CH_2CH{=}CH_2$

XX, R = $N(CH_3)CH_2C{\equiv}CH$
XXI, R = $NHC(=NH)NH_2$
XXII, R = 
XXIII, R = 
XXIV, R = $(CH_2)_3N(CH_3)$

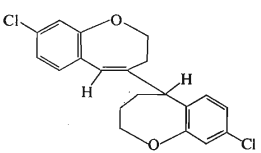
of amine *XXII* to the olefinic derivative *XXV* (the activation group in the case of the donor as well as the acceptor being aryl), its structure being probably that of *XXXI*. This structure is also in agreement with the course of the reaction with ethyl chloroformate when the methylpiperazine residue is split off in the form of 1-methyl-4-ethoxycarbonylpiperazine[22] (isolated and characterized as hydrochloride) and compound $C_{20}H_{19}Cl_3O_2$ is formed for which formula *XXXII* is suggested.

Reaction of ketone *I* with 3-dimethylaminopropylmagnesium chloride yielded the amino alcohol *XXXIII* (yielding a stable crystalline hydrochloride), which was dehydrated by boiling with 3N-H_2SO_4. Chromatography of a sample of the crude base on a thin layer of alumina showed that we are dealing here with a mixture of two bases (one strongly predominating) with rather close R_F values. Separation of the two bases was achieved by fractional crystallization of the picrates. The base predominating in the mixture was identified by its UV spectrum (λ_{max} 251 nm) as isomer *XXVI* with an endocyclic double bond while the minor component is the

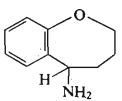


XXV, R = H
XXVI, R = $(CH_2)_3N(CH_3)_2$

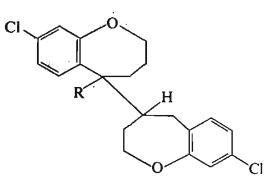
XXVII, R = $(CH_2)_3NHCH_3$
XXVIII, R = C_6H_5



XXIX

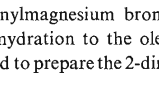


XXX



XXXI, R = N⟨ ⟩NCH$_3$
XXXII, R = Cl

isomer *XXXVII* with an exocyclic double bond (λ_{max} 239 nm). Reduction of the aminoalcohol *XXXIII* with hydrogen iodide in acetic acid yielded the saturated base *XXIV*. Reaction of aminoalcohol *XXXIII* with ethyl chloroformate yielded a neutral substance consisting mostly of the hydroxycarbamate *XXXIV*. The simultaneous formation of the hydrochloride of the starting compound *XXXIII* indicated that a partial dehydration took place. This was confirmed by alkaline hydrolysis of the crude carbamate which resulted in a major amount of amino alcohol *XXXV* plus a small amount of unsaturated secondary amine which, on the basis of its UV spectrum (λ_{max} 246 nm) is ascribed a structure with an endocyclic double bond (*XXVII*). A discussion of the UV spectra of analogous olefins may be found in ref.[13,23]. Reaction of ketone *I* with phenylmagnesium bromide yielded the tertiary alcohol *XXXVI* which distils under dehydration to the olefinic derivative *XXVIII*. A conventional technique was then used to prepare the 2-dimethylaminoethyl ether *XXXVIII* from alcohol *XXXVI*.



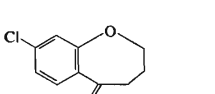
XXXIII, R = $(CH_2)_3N(CH_3)_2$

XXXIV, R = $(CH_2)_3N(CH_3)COOC_2H_5$

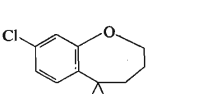
XXXV, R = $(CH_2)_3NHCH_3$

XXXVI, R = C_6H_5

Mannich's reaction in the 1-benzoxepin series using dimethylamine was studied also by Dann and Arndt[2] and, more recently, by De Stevens[11]. In the present work we carried out Mannich's reaction of ketone *I* with piperidine and aqueous formaldehyde in ethanol, as well as with piperidine hydrochloride and paraformaldehyde in ethanol. In both cases, we obtained the expected Mannich base *XXXIX*, the formation of which was accompanied by a small amount of a neutral crystalline compound $C_{22}H_{18}Cl_2O_4$ which is assumed to have structure *XLIII* (for analogy see also ref.[14]). Reduction of the amino ketone *XXXIX* with sodium borohydride in aque-



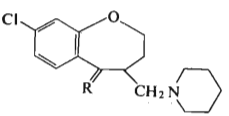
XXXVII



XXXVIII

ous methanol gives rise to a mixture of two racemic amino alcohols *XL*, from which individual compounds could not be isolated even in the form of salts. Acetylation

of the crude base with acetic anhydride, distillation and crystallization of the hydrochloride yielded one individual racemate of the acetoxy derivative *XLI*, and the mother liquor a single pure racemate of the hydrochloride of amino alcohol *XL*. We assume that in the case of the acetoxy derivative we are dealing with a *trans* isomer while the drastic acylation-resisting alcohol, *XL*, might be a *cis* isomer, the hydroxyl function of which is sterically hindered by the surrounding substituents. Reaction of the Mannich base *XXXIX* with phenylmagnesium bromide produced a 40% yield of a crystalline and apparently homogeneous amino alcohol *XLII* in which the large substituents (phenyl and piperidinomethyl) are apparently *trans* to each other. This is also supported by the smooth dehydration with alcoholic solution of hydrochloric acid which yields practically 90% of crystalline 4-(piperidinomethyl)-5-phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XLIV*).

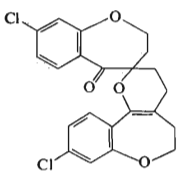


XXXIX, R = O

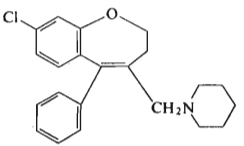
XL, R = H, OH

XLI, R = H, $OCOCH_3$

XLII, R = C_6H_5, OH



XLIII



XLIV

The following compounds were tested pharmacologically (acute toxicity for mice LD_{50} in mg/kg and way of application are shown) using mostly a broader spectrum of tests in methods of general screening: *III* (2000 *p.o.*), *V* (1500 *p.o.*), *IX*-HCl (60 *i.v.*), *XIII*-HCl (75 *i.v.*), *XV*-HCl (45 *i.v.*), *XVI* (2500 *p.o.*), *XVII*-hydrogen maleate (40 *i.v.*), *XVIII*-HCl (25 *i.v.*), *XIX*-HCl (90 *i.v.*), *XX*-HCl (125 *i.v.*), *XXI*-hemisulfate, *XXII*-di(hydrogen maleate) (75 *i.v.*), *XXIII*-maleate (150 *i.v.*), *XXVI*-hydrogen maleate (80 *i.v.*), *XXXI*-2 HCl (2000 *p.o.*), *XXXIII*-HCl (87·5 *i.v.*), *XXXVIII*-HCl (41 *i.v.*), *XXXIX*-hydrogen maleate (40 *i.v.*), *XLI*-HCl (60 *i.v.*), *XLII*-HCl (2000 *p.o.*), and *XLIV*-HCl (75 *i.v.*).

In all the compounds tested one may observe the practically complete absence of neurotropic, especially centrally neurotropic effects. From this point of view, we investigated especially compound *XXXVIII* which may be considered as an analogue of the antihistaminic and central depressant basic benzhydryl ethers. At the doses used the compound has no central depressant activity (rotating-rod test in mice, potentiation of thiopental sleep in mice), no antihistamine activity (*in vivo*), no antiserotonin activity (in rats *in vivo*), no antireserpine activity (ptosis in mice), no cataleptic activity (rats) and no anticonvulsant activity (against pentetrazole). As one of a few compounds tested it showed antimicrobial activity *in vitro* against several microorganisms (the minimal inhibitory concentrations in μg/ml are shown): *Streptococcus β-haemolyticus* (100), *Staphylococcus pyogenes aureus* including its penicillin-resistant strain (50), *Klebsiella pneumoniae* (50), *Escherichia coli* (100), *Salmonella typhi abdominalis* (100), *Proteus vulgaris* (100). With compound *IX* we observed an indication of the spasmolytic effect in *in vitro* tests (rat duodenum), both against barium chloride and acetylcholine contractions. Compounds *XXVI* and *XXXIX* were active in the test of infiltration anaesthesia, the first-named being more active than procaine, the second being about equally active. In a greater number of compounds of this group the test in rats, using doses 5–30 mg/kg *i.v.*, showed a slight hypotensive activity (*XIII*, *XV*, *XIX*, *XXIII*, *XXVI*, *XLIV*), in some cases even protracted (*XVII*, *XVIII*, *XXII*, *XXXIII*, *XLI*). In some compounds we demonstrated also the adrenolytic activity (*XIII*, *XXVI*). With compound *XLI* we observed a sign of diuretic and analgesic activity in tests in mice. With compounds *III* and *V* it was not possible to demonstrate the expected hypocholesterolaemic activity. Compound *V* at an oral dose of 300 mg/kg in rats significantly decreases the blood glucose level. Compounds *III* and *XVI* display in an oral dose of 300 mg/kg in rats a clear antiinflammatory activity in the kaolin edema test. Still more pronounced in this respect is the activity of compound *XXXIII*: at an oral dose of 200 mg/kg or at a subcutaneous dose of 50 mg/kg it is significantly active in the kaolin edema test in rats (a model of acute inflammation); on the other hand, it is practically ineffective with subchronic inflammations.

Compound *XX* was evaluated from the point of view of the fact that it is an analogue of "pargyline"[24]. At a dose of 12 mg/kg *i.v.* it blocks, similarly to pargyline, the potentiation of thiopental sleep by reserpine in rats. The compound is more active than pargyline in inhibiting the blockade of motor activity of mice brought about by reserpine, and in the antireserpine effect on eyelid ptosis in mice. In rats in urethane narcosis it shows a similar biphasic effect on blood pressure as pargyline, *i.e.* it brings about a sharp drop and subsequent rise, lasting for about 1 hour. In agreement with pargyline, it increases the level of 5-hydroxytryptamine in the brain which demonstrates its inhibitory effect against monoamine oxidase. Further support for this is provided by the potentiation of tryptamine convulsions. At a dose of 15 mg/kg *s.c.* it does not bring about any more substantial drop of blood pressure

in rats with experimental renal hypertension. At a concentration of 100 μg/ml *in vitro* it brings about inhibition of growth of *Staphylococcus pyogenes aureus* and *Mycobacterium tuberculosis* $H_{37}Rv$.

Finally, mention should be made of the guanidine derivative *XXI* which was evaluated as an analogue of "guanethidine"[25]. In rats with slight DOCA hypertension the compound when applied *i.v.* brings about similar reactions of the blood pressure as does guanethidine which, however, is quantitatively more effective. In cats it shows a short-lived hypotensive effect and in monkeys when administed *per os*, it does not affect the pressor response to ephedrine.

Even if a number of the compounds described here possessed indications of interesting activities the experimental findings did not justify in any single case further detailed pharmacological or toxicological studies.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block; the samples were dried in the usual way. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200 G spectrophotometer.

4-(3-Chlorophenoxy)butyric Acid (*II*)

Butanol was distilled from a mixture of 90 ml 1-butanol, 15 g sodium hydroxide and 46 g 3-chlorophenol[17,18] (b.p. 110°C/12 Torr) until the temperature reached 155°C. After cooling to 150°C, 30·8 g 4-butyrolactone were added and distillation of the mixture continued until 160°C were reached. The mixture was then refluxed for 4 h, cooled, dissolved in 530 ml water and butanol was removed together with the nonreacted 3-chlorophenol by steam distillation. The remaining solution was decolourized by filtration with charcoal and the filtrate was made acid under stirring with dilute hydrochloric acid; 60·4 g (80%), m.p. 51—53°C. For the product, prepared by a different procedure, literature[16] gives a m.p. of 51—52°C.

Ethyl 4-(3-chlorophenoxy)butyrate (*III*)

A mixture of 20 g acid *II*, 70 ml benzene, 2·5 ml ethanol and 0·9 ml sulfuric acid was subjected to azeotropic distillation using a water separator and an attachment for recycling the benzene used. The mixture was distilled for 4 h and, during this period, 10·5 ml ethanol were added dropwise. After cooling, the mixture was washed with water and 5% sodium carbonate, dried with calcium chloride and distilled: 17·0 g (75%), b.p. 180°C/15 Torr. For $C_{12}H_{15}ClO_3$ (242·7) calculated: 59·38% C, 6·23% H, 14·61% Cl; found: 59·32% C, 6·18% H, 14·84% Cl.

4-(3-Chlorophenoxy)butyryl Chloride (*IV*)

A mixture of 250 ml benzene, 30 g *II* and 22 g thionyl chloride was refluxed for 2 h and then distilled: 25·7 g (79%), b.p. 138°C/0·7 Torr. For $C_{10}H_{10}Cl_2O_2$ (233·1) calculated: 51·53% C, 4·32% H, 30·42% Cl; found: 51·83% C, 4·47% H, 30·16% Cl.

4-(3-Chlorophenoxy)butyramide (*V*)

A solution of 25·75 g chloride *IV* in 200 ml ether was cooled with ice and stirred while being saturated with gaseous ammonia (1 h). The ether was then evaporated, the residue dissolved

in chloroform and the solution washed with water and with a solution of sodium carbonate. Evaporation yielded 19·4 g (80%) product; m.p. 90—91°C (benzene–light petroleum or aqueous ethanol). For $C_{10}H_{12}ClNO_2$ (213·7) calculated: 56·22% C, 5·66% H, 16·59% Cl, 6·56% N; found: 56·05% C, 5·72% H, 16·77% Cl, 6·58% N.

N,N-Diethyl-4-(3-chlorophenoxy)butyramide (*VI*)

Diethylamine (25 g) was added dropwise to a solution of 21·4 g chloride *IV* in 100 ml ether under stirring and the mixture was refluxed for 8 h. After cooling, it was washed with water and with a solution of sodium carbonate, the ether was evaporated and the residue (9·6 g) was redistilled; b.p. 163—165°C/0·6 Torr. For $C_{14}H_{20}ClNO_2$ (269·8) calculated: 62·34% C, 7·47% H, 13·14% Cl, 5·19% N; found: 62·64% C, 7·70% H, 13·17% Cl, 5·08% N.

N-(2-Diethylaminoethyl)-4-(3-chlorophenoxy)butyramide (*VII*)

2-Diethylaminoethylamine (5·0 g) was added to a solution of 8·25 g chloride *IV* in 30 ml ether under stirring and external cooling with ice. The mixture was left to stand at room temperature overnight, 20 ml benzene was then added and the mixture was washed first with 50 ml 5% sodium hydroxide and then with water. After drying (potassium carbonate) the solvents were evaporated at reduced pressure and the residue (9·6 g) was redistilled; b.p. 196—200°C/0·4 Torr. UV spectrum: λ_{max} 217·5 nm (log ε 3·948). IR spectrum: 683, 774 and 881 (1,3-disubstituted benzene), 1043, 1071, 1232 and 1249 (Ar—O—R), 1552, 1580, 1597 and 1650 (CONH), 3314 cm^{-1} (NH). For $C_{16}H_{25}ClN_2O_2$ (312·8) calculated: 61·43% C, 8·05% H, 11·33% Cl, 8·96% N; found: 60·94% C, 8·27% H, 11·57% Cl, 8·78% N.

8-Chloro-2,3-dihydro-4*H*-1-benzoxepin-5-one (*I*)

Acid *II* (21·5 g) was added under stirring at 80—90°C over a period of 1 h to polyphosphoric acid prepared from 129 g phosphorus pentoxide and 100 ml phosphoric acid (d = 1·8). The mixture was stirred at that temperature for 1·5 h, partly cooled, decomposed by pouring over 300 ml water and ice and extracted with a mixture of benzene and chloroform. The extract was washed with 10% sodium carbonate and water and evaporated at reduced pressure. Distillation of the residue yielded 15·5 g (79%) product boiling at 107°C/0·4 Torr. If the amount of polyphosphoric acid was reduced to one-half the yield dropped to 66%. UV spectrum: λ_{max} 216 nm (log ε 4·271), 253 nm (4·023), 298·5 nm (3·427). IR spectrum (substance, CCl_4): 771 and 827 (1,2,4-trisubstituted benzene), 1219 (Ar—O—R), 1599 (Ar), 1691 cm^{-1} (CO conjugated). For $C_{10}H_9ClO_2$ (196·6) calculated: 61·08% C, 4·61% H, 18·03% Cl; found: 61·15% C, 4·69% H, 17·78% Cl.

Oxime (VIII) was prepared in an almost theoretical yield by refluxing for 6 h a mixture of 42 g ketone, 350 ml ethanol, 28 g hydroxylamine hydrochloride and 56 g anhydrous potassium carbonate. M.p. 117—119°C (benzene–light petroleum). For $C_{10}H_{10}ClNO_2$ (211·7) calculated: 56·75% C, 4·76% H, 16·75% Cl, 6·62% N; found: 56·95% C, 4·85% H, 16·74% Cl, 6·72% N.

O-(2-Dimethylaminoethyl)-5-oximino-8-chloro-2,3-dihydro-4*H*-1-benzoxepin (*IX*)

Oxime *VIII* (5·3 g) was dissolved in a boiling solution of 3·5 g sodium in 50 ml ethanol and, after cooling, a solution of 4·3 g 2-dimethylaminoethyl chloride hydrochloride in 50 ml ethanol was added dropwise. The mixture was refluxed for 4 h, ethanol was then evaporated at reduced pressure, the residue was decomposed with water and extracted with benzene. After washing the extract with water and drying, benzene was evaporated. The nonhomogeneous residue obtained

(5·8 g) was treated with anhydrous hydrogen chloride in ether to yield 1·1 g (31%) *hydrochloride* of the desired compound; m.p. 189—190°C (ethanol–ether). UV spectrum: λ_{max} 215 nm (log ε 4·299), 252 nm (4·164), 290 nm (3·541). IR spectrum: 835 and 889 (1,2,4-trisubstituted benzene), 1 211 (Ar—O—R), 1 595 (Ar), 1 620 cm^{-1} (C=N). For $C_{14}H_{20}Cl_2N_2O_2$ (319·2) calculated: 52·67% C, 6·32% H, 22·21% Cl, 8·78% N; found: 52·71% C, 6·43% H, 22·23% Cl, 8·48% N.

9-Chloro-2,3,4,5-tetrahydro-1,5-benzoxazocin-6-one (*X*)

Phosphorus pentachloride (7·0 g) was added to a solution of 7·0 g oxime *VIII* in 10 ml ether and 20 ml benzene and the mixture was refluxed for 3 h. After cooling, it was decomposed with 350 ml ice-cold water and made slightly alkaline with potassium carbonate. The separated organic layer was dried and evaporated. After dissolving the inhomogeneous residue (5·0 g) in a mixture of 20 ml benzene and 20 ml ether a small amount of substance melting at 213—215°C (benzene) crystallized. UV spectrum: λ_{max} 238 nm (log ε 4·126), 279 nm (3·386). IR spectrum 822 and 880 (1,2,4-trisubstituted benzene), 1 210 (Ar—O—R), 1 502 and 1 670—1 680 (Ar—CONH—R), 1 599 (Ar), 3 283 cm^{-1} (NH). For $C_{10}H_{10}ClNO_2$ (211·7) calculated: 56·75% C, 4·76% H, 16·75% Cl, 6·62% N; found: 57·02% C, 4·90% H, 17·39% Cl, 6·32% N.

11-Chloro-2,3-dihydro-4*H*-tetrazolo[5,1-*e*]-1,6-benzoxazocine (*XI*)

2·1 g sodium azide was added under stirring over a period of 3 h to a solution of 5·5 g ketone *I* in 22 ml sulfuric acid at 20—30°C. After 12 h of standing at room temperature it was diluted with 500 ml water and extracted with chloroform. Evaporation of the extract yielded 1·5 g product for which structure *XI* is preferred on the basis of analogy[26]; m.p. 168—169°C (ethanol). UV spectrum: λ_{max} 213 nm (log ε 4·353), 239 nm (4·109), 282 nm (3·370), 293 nm (3·293). IR spectrum: 770, 827 and 869 (1,2,4-trisubstituted benzene), 1 220 (Ar—O—R), 1 578 (Ar), 1 611 cm^{-1} (C=N, N=N). For $C_{10}H_9ClN_4O$ (236·7) calculated: 50·75% C, 3·83% H, 14·98% Cl, 23·68% N; found: 51·08% C, 3·89% H, 15·06% Cl, 23·89% N.

8-Chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XII*)

2·3 g sodium borohydride was added to a suspension of 10·0 g ketone *I* in 110 ml ethanol under stirring and the mixture was refluxed for 30 min. Ethanol was then evaporated at reduced pressure, the residue was dissolved in chloroform, the solution was washed with 100 ml 1M-HCl and water, dried with potassium carbonate and evaporated to dryness. The residue was recrystallized from a mixture of benzene and light petroleum; 9·0 g (89%) m.p. 62—63°C. UV spectrum λ_{max} 219 nm (log ε 3·929), 269 nm (2·979), 275 nm (3·002). IR spectrum: 814, 870, 898, (1,2,4-trisubstituted benzene), 1 040 and 1 053 (cyclic secondary alcohol), 1 223 (Ar—O—R), 1 574 and 1 598 (Ar), 3 250 and 3 330 cm^{-1} (OH). For $C_{10}H_{11}ClO_2$ (198·6) calculated: 60·46% C, 5·58% H, 17·85% Cl; found: 60·45% C, 5·58% H, 17·82% Cl.

5-(2-Dimethylaminoethoxy)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XIII*)

A mixture of 50 ml benzene, 2·9 g sodium amide and 8·1 g alcohol *XII* was stirred for 15 min. 5·3 g 2-dimethylaminoethyl chloride was then added and the mixture was refluxed under stirring for 8 h. After cooling, it was decomposed with water and the benzene solution was evaporated. The residue (12 g) was converted by direct treatment with hydrogen chloride in a mixture of acetone and ether to a *hydrochloride*: 10·0 g (80%), m.p. 136—137°C (acetone–ether). For $C_{14}H_{21}$. $.Cl_2NO_2$ (306·2) calculated: 54·91% C, 6·91% H, 23·16% Cl, 4·57% N; found: 54·59% C, 7·01% H, 23·31% Cl, 4·64% N.

Hydrogen maleate was prepared from the base liberated in the usual way. M.p. 94°C (acetone–ether). For $C_{18}H_{24}ClNO_6$ (385·9) calculated: 56·03% C, 6·27% H, 9·19% Cl, 3·63% N; found: 55·95% C, 6·29% H, 9·32% Cl, 3·73% N.

5,8-Dichloro-2,3,4,5-tetrahydro-1-benzoxepin (*XIV*)

A solution of 16·0 g alcohol *XII* in 145 ml benzene, to which 7·3 g powdery anhydrous calcium chloride was added, was saturated for 2·5 h with gaseous hydrogen chloride at room temperature. After standing overnight it was filtered and the filtrate was evaporated *in vacuo* at maximum temperature of the bath equal to 40°C. The oily residue (16·7 g) represents a crude product which was used without further purification.

When attempting to distil a part of the product (8·0 g) it was decomposed and 0·6 g of a lower fraction (b.p. 85—88°C/0·6 Torr) and 5·2 g of a higher fraction (b.p. 220°C/1 Torr) was obtained.

The lower fraction represents 8-*chloro*-2,3-*dihydro*-1-*benzoxepin* (XXV). For $C_{10}H_9ClO$ (180·6) calculated: 66·49% C, 5·02% H, 19·63% Cl; found: 66·67% C, 5·14% H, 19·63% Cl. The higher fraction is assumed to correspond on the basis of its analysis and spectra to 4-(8-*chloro*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-5-*yl*)-8-*chloro*-2,3-*dihydro*-1-*benzoxepin* (XXIX). UV spectrum: λ_{max} 218 nm (log ε 4·600), 253 nm (4·317), 267 nm (4·423), 296·5 nm (3·808), 306 nm (3·755), 333 nm (3·373). IR spectrum: 810, 872 and 894 (1,2,4-trisubstituted benzene), 1 224 and 1 304 (Ar—O—R), 1 567 and 1 595 cm^{-1} (Ar). NMR spectrum ($CDCl_3$): δ 6·93 (6 aromatic protons), 6·04 (1 H in Ar—CH—C), 3·90—4·40 (4 H, twice —CH_2O—), 3·70 (1 H in Ar—CH—), 2·60 (2 H in =C—CH_2), 1·85—2·15 (4 H in —CH_2CH_2—in position 3, 4). Molecular weight (mass spectrum): 360 for $^{35}Cl_2$ (triplet of isotopic satellites demonstrates the presence of two chlorine atoms per molecule). For $C_{20}H_{18}Cl_2O_2$ (361·3) calculated: 66·49% C, 5·02% H, 19·63% Cl; found: 66·99% C, 5·10% H, 19·52% Cl.

5-Amino-2,3,4,5-tetrahydro-1-benzoxepin (*XXX*)

5·8 g sodium was added to a solution of 5·0 g oxime *VIII* in 50 ml ethanol and the mixture was refluxed until the metal dissolved. After cooling, it was diluted with 200 ml water and extracted with benzene. The basic product from the extract was transferred by shaking into 50 ml 15% hydrochloric acid. The separated aqueous solution was made alkaline with 20% sodium hydroxide and the base was isolated by extraction with ether: 1·6 g oily substance.

Hydrochloride, m.p. 245—247°C (ethanol–ether). For $C_{10}H_{14}ClNO$ (199·7) calculated: 60·15% C, 7·07% H, 17·76% Cl, 7·01% N; found: 60·22% C, 7·25% H, 17·86% Cl, 7·07% N.

5-Formamido-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XVI*)

A mixture of 5·0 g ketone *I* and 5·3 g formamide was heated for 12 h to 180°C and, during this period, 12 ml 98% formic acid was gradually added. After cooling, it was diluted with 100 ml water and extracted with ether. The residue after evaporation of the extract crystallized from 15 ml ethanol to yield 5·0 g (87%) product, m.p. 125—127°C. UV spectrum: λ_{max} 219 nm (log ε 4·022), 268 nm (3·125), 276 nm (3·125). IR spectrum: 839, 885 (1,2,4-trisubstituted benzene), 1 542 and 1 663 (—NHCHO), 1 600 (Ar), 3 290 cm^{-1} (NH). For $C_{11}H_{12}ClNO_2$ (225·7) calculated: 58·54% C, 5·36% H, 15·71% Cl, 6·21% N; found: 58·68% C, 5·48% H, 15·67% Cl, 6·24% N.

5-Amino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XV*)

A mixture of 22·5 g amide *XVI* and 225 ml concentrated hydrochloric acid was heated in an oil bath. At 120°C the reaction took place (15 min). The mixture was then refluxed for 6 h in a bath

at 150°C. Upon cooling, 22·1 g (95%) *hydrochloride*, melting at 293°C under decomposition (ethanol–ether) crystallized. For $C_{10}H_{13}Cl_2NO$ (234·1) calculated: 51·30% C, 5·60% H, 30·29% Cl, 5·98% N; found: 51·59% C, 5·71% H, 30·56% Cl, 5·98% N. Decomposition of the aqueous suspension of the hydrochloride with a 20% solution of sodium hydroxide and extraction with benzene yielded the base, b.p. 120—133°C/0·4 Torr.

Hemisulfate, m.p. 224—227°C (aqueous ethanol). For $C_{10}H_{12}ClNO \cdot 0{\cdot}5\ H_2SO_4$ (246·7) calculated: 14·37% Cl, 5·68% N, 6·48% S; found: 13·95% Cl, 5·30% N, 6·36% S.

5-Methylamino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XVII*)

Reduction of 23·0 g amide *XVI* with 8·1 g lithium aluminium hydride in 300 ml tetrahydrofuran and conventional treatment of the reaction mixture yielded 14·85 g (69%) base boiling at 117 to 120°C/0·6 Torr. For $C_{11}H_{14}ClNO$ (211·7) calculated: 62·41% C, 6·66% H, 16·75% Cl, 6·62% N; found: 62·66% C, 6·75% H, 16·73% Cl, 6·63% N. The same product (b.p. 111—116°C/0·4 Torr) was obtained by heating ketone *I* with methylamine formate to 170°C.

Hydrochloride, m.p. 198—200°C (ethanol–ether). For $C_{11}H_{15}Cl_2NO$ (248·2) calculated: 53·24% C, 6·09% H, 28·58% Cl, 5·64% N; found: 52·95% C, 6·11% H, 28·72% Cl, 5·69% N.

Hydrogen maleate, m.p. 188—191°C (ethanol). For $C_{15}H_{18}ClNO_5$ (327·8) calculated: 54·96% C, 5·53% H, 10·82% Cl, 4·27% N; found: 55·37% C, 5·69% H, 10·98% Cl, 4·24% N.

5-Diethylamino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XVIII*)

A mixture of 6·1 g amine *XV*, 8·45 g 98% formic acid and 7·5 g 36% solution of formaldehyde was stirred and heated to 100°C for 8 h. After cooling, it was made acid with 56 ml 20% hydrochloric acid, diluted with water and washed with ether. The acid aqueous solution was made alkaline with 40% sodium hydroxide and the base was isolated by extraction with ether: 4·05 g (59%), b.p. 123°C/0·9 Torr. For $C_{12}H_{16}ClNO$ (225·7) calculated: 63·86% C, 7·14% H, 15·71% Cl, 6·20% N; found: 63·33% C, 7·19% H, 16·10% Cl, 6·29% N.

Hydrochloride, m.p. 197—201°C (ethanol–ether). For $C_{12}H_{17}Cl_2NO$ (262·2) calculated: 54·97% C, 6·54% H, 27·05% Cl, 5·34% N; found: 54·92% C, 6·28% H, 26·79% Cl, 5·63% N.

5-(N-Methyl-N-allylamino)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XIX*)

A mixture of 12·0 g amine *XVII*, 200 ml 1-butanol, 8·2 g allyl bromide and 9·2 g anhydrous potassium carbonate was heated under stirring for 12 h to 110—120°C. After filtering the inorganic salts and washing them with chloroform, the filtrate was distilled. A total of 12·05 g (85%) of a not fully homogeneous base was obtained which was converted in the usual way to picrate. Fractional crystallization of the picrate yielded 0·6 g light-yellow fraction melting at 139—141°C which was not identified, and 13·9 g of an orange fraction melting at 151—153°C (acetone–ethanol) which represents the picrate of the desired base. For $C_{20}H_{21}ClN_4O_8$ (480·9) calculated: 49·95% C, 4·40% H, 7·38% Cl, 11·65% N; found: 50·16% C, 4·59% H, 7·15% Cl, 11·87% N. The base liberated from this picrate in the usual way boiled at 130°C/0·9 Torr. For $C_{14}H_{18}ClNO$ (251·8) calculated: 66·79% C, 7·20% H, 14·08% Cl, 5·56% N; found: 67·29% C, 7·40% H, 13·66% Cl, 5·54% N.

Hydrochloride, m.p. 180—182°C (acetone–ether–ethanol). For $C_{14}H_{19}Cl_2NO$ (288·2) calculated: 58·34% C, 6·65% H, 24·60% Cl, 4·86% N; found: 58·44% C, 6·58% H, 24·20% Cl, 5·02% N.

5-(N-Methyl-N-propargylamino)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XX*)

Similarly to the preceding case, a reaction of 9·0 g amine *XVII*, 6·1 g propargyl bromide and 6·9 g potassium carbonate was conducted in 150 ml 1-butanol. A total of 9·0 g inhomogeneous product was obtained, from which fractional distillation yielded 3·55 g base boiling at 127—133°C/0·2 Torr. For $C_{14}H_{16}ClNO$ (249·7) calculated: 67·33% C, 6·46% H; found: 67·87% C, 7·03% H.

Hydrochloride, m.p. 176—177°C (acetone–ethanol–ether). For $C_{14}H_{17}Cl_2NO$ (286·2) calculated: 58·75% C, 5·98% H, 24·78% Cl, 4·89% N; found: 59·06% C, 6·28% H, 24·61% Cl, 4·81% N.

5-Guanidino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXI*)

A mixture of 9·4 g amine *XV*, 6·6 g S-methylisothiuronium sulfate and 6·5 ml water was refluxed under stirring for 7 h. After dilution with water and cooling, the precipitated inhomogeneous product was filtered and purified by several-fold crystallization from aqueous ethanol; *hemisulfate* melting at 284—286°C. For $C_{11}H_{14}ClN_3O.0{\cdot}5\,H_2SO_4$ (288·7) calculated: 45·76% C, 5·24% H, 12·28% Cl, 14·55% N, 5·54% S; found: 46·11% C, 5·38% H, 12·36% Cl, 14·82% N, 5·72% S.

5-(4-Methylpiperazino)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXII*)

A mixture of 8·7 g crude chloride *XIV* and 19·7 ml 1-methylpiperazine was heated for 3 h to 105°C. After cooling, it was diluted with 100 ml water and extracted with benzene. The extract was washed with water and the base was extracted with 3M-HCl. From a separated solution of the hydrochloride, the base was liberated again by alkalinization with a 20% solution of sodium hydroxide. It was isolated by extraction with ether; 2·3 g (21%) oily substance. The crude base was directly converted to salts.

Dihydrochloride monohydrate, m.p. 204—206°C (ethanol–ether). For $C_{15}H_{25}Cl_3N_2O_2$ (371·7) calculated: 48·47% C, 6·78% H; found: 48·44% C, 7·14% H.

Di(hydrogen maleate), m.p. 182—183°C (ethanol–acetone–ether). For $C_{23}H_{29}ClN_2O_9$ (513·0) calculated: 53·85% C, 5·70% H, 6·91% Cl, 5·46% N; found: 54·03% C, 5·84% H, 7·10% Cl, 5·39% N.

5-(4-Phenylpiperazino)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXIII*)

A solution of 21·9 g crude chloride *XIV* and 32·6 g 1-phenylpiperazine[21] in 50 ml chloroform was refluxed for 6 h. Similarly to the preceding case, a crude base was isolated which was first freed of unreacted 1-phenylpiperazine (16·6 g, b.p. 105—112°C/0·6 Torr). The distillation residue crystallized after dissolving in 15 ml benzene and adding 5 ml light petroleum; 5·0 g, m.p. 119°C (ethanol). For $C_{20}H_{23}ClN_2O$ (342·9) calculated: 70·06% C, 6·76% H, 10·34% Cl, 8·17% N; found: 69·77% C, 6·92% H, 10·55% Cl, 8·45% N.

Dihydrochloride, m.p. 202—206°C (ethanol–ether). For $C_{20}H_{25}Cl_3N_2O$ (415·8) calculated: 57·77% C, 6·06% H, 25·58% Cl, 6·74% N; found: 57·49% C, 6·12% H, 25·04% Cl, 7·34% N.

Dihydrochloride hemihydrate, m.p. 176—179°C (ethanol–ether). For $C_{20}H_{25}Cl_3N_2O.0{\cdot}5\,H_2O$ (424·8) calculated: 56·55% C, 6·17% H, 25·04% Cl, 6·59% N; found: 56·51% C, 6·28% H, 24·57% Cl, 7·31% N.

Maleate monohydrate, m.p. 173—174°C (acetone–ethanol–ether). For $C_{24}H_{29}ClN_2O_6$ (477·0) calculated: 60·44% C, 6·13% H, 7·43% Cl, 5·87% N; found: 60·73% C, 5·81% H, 7·26% Cl, 6·16% N.

5-(4-Methylpiperazino)-5-(8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXXI*)

A mixture of 30 g crude chloride *XIV* and 26·8 g 1-methylpiperazine was heated for 5 h to 105°C. After cooling, it was diluted with benzene and extracted with excess 10% hydrochloric acid. A total of 8·7 g salt precipitated, which was crystallized from a mixture of 90% ethanol and ether; m.p. 245—250°C under decomposition. According to analysis we are dealing here with a *dihydrochloride monohydrate*. For $C_{25}H_{34}Cl_4N_2O_3$ (552·4) calculated: 54·36% C, 6·20% H, 25·67% Cl; found: 54·23% C, 6·54% H, 25·56% Cl.

Decomposition of the hydrochloride with a solution of sodium hydroxide and extraction with chloroform yielded a base melting at 182—184°C (ethanol). UV spectrum: λ_{max} 224 nm (log ε 4·220) 273 nm (3·298), 279 nm (3·193). IR spectrum: 837 and 878 (1,2,4-trisubstituted benzene), 1 290 (Ar—O—R), 1 568 and 1 593 cm^{-1} (Ar). Mass spectrum: molecular weight 460 for $^{35}Cl_2$; the abundant ions *m/e* 279, containing one chlorine atom, ions 181, also containing one chlorine atom, and ions *m/e* 99 without chlorine atom, support the assumed structure *XXXI*; heterocycles containing oxygen are most likely linked through at least one benzyl carbon. For $C_{25}H_{30}Cl_2N_2O_2$ (461·5) calculated: 65·07% C, 6·55% H, 15·37% Cl, 6·07% N; found: 64·97%C, 6·54% H, 15·31% Cl, 6·28% N. *Di(hydrogen maleate)*, m.p. 147—149°C (ethanol–ether). For $C_{33}H_{38}Cl_2N_2O_{10}$ (693·6) calculated: 57·15% C, 5·52% H, 10·22% Cl, 4·04% N; found: 57·18%C, 5·58% H, 9·96% Cl, 4·06% N.

5,8-Dichloro-5-(8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)-2,3,4,5-tetrahydro-1-benzoxepin (*XXXII*)

3·0 g base *XXXI* was added to a boiling solution of 3·0 g ethyl chloroformate in 25 ml benzene and the mixture was refluxed for 2 h. After cooling, filtration yielded 0·35 g precipitated 1-*ethoxycarbonyl-4-methylpiperazine hydrochloride*, m.p. 170—171°C (ethanol–ether). Ref.[22] gives m.p. 168·5—169°C. For $C_8H_{17}ClN_2O_2$ (208·7) calculated: 46·04% C, 8·21% H, 16·99% Cl, 13·42% N; found: 45·81% C, 8·40% H, 17·51% Cl, 13·42% N.

The benzene filtrate was washed with 10% sulfuric acid and water and evaporated. The residue after dissolving in 10 ml boiling cyclohexane yielded upon cooling 1·5 g compound melting at 154—157°C (benzene–light petroleum). UV spectrum: λ_{max} 221 nm infl. (log ε 4·243), 273 nm (3·452), 279 nm (3·452). IR spectrum: 816, 821, 880 (1,2,4-trisubstituted benzene), 1 221 and 1 242 (Ar—O—R), 1 569 and 1 596 cm^{-1} (Ar). Mass spectrum: molecular weight 396 for chlorine isotope $^{35}Cl_3$ (quadruplet of isotopically linked ions demonstrates the presence of three chlorine atoms): one of the chlorine atoms is readily eliminated as HCl; mass spectrum is in agreement with structure *XXXII*. For $C_{20}H_{19}Cl_3O_2$ (397·8) calculated: 60·39% C, 4·82% H, 26·74% Cl; found: 60·57% C, 4·89% H, 26·58% Cl.

5-(3-Dimethylaminopropyl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XXXIII*)

A solution of 9·8 g ketone *I* in 20 ml ether was added dropwise to a Grignard reagent prepared in the usual way[13] from 9·12 g 3-dimethylaminopropyl chloride and 1·8 g magnesium in 50 ml tetrahydrofuran. The mixture was refluxed under stirring for 4 h. After cooling it was decomposed with saturated ammonium chloride and extracted with benzene. The extract was thoroughly washed with water, the basic product was transferred into 10% ice-cold hydrochloric acid, immediately liberated by alkalinization and isolated by extraction with ether: 8·7 g, m.p. 99·5—101°C (light petroleum). UV spectrum: λ_{max} 220 nm (log ε 3·984), 270 nm (3·133), 276 nm (3·153). IR spectrum: 831, 890 (1,2,4-trisubstituted benzene), 1 039 and 3 450 (OH), 1 220 (Ar—O—R), 1 595 (Ar), 2 713 and 2 805 cm^{-1} (N—CH_3). For $C_{15}H_{22}ClNO_2$ (283·8) calculated: 63·48% C, 7·81% H, 12·49% Cl, 4·94% N; found: 63·18% C, 8·01% H, 12·45% Cl, 4·82% N.

Hydrochloride, m.p. 203°C (ethanol–ether). For $C_{15}H_{23}Cl_2NO_2$ (320·3) calculated: 56·25% C, 7·24% H, 22·14% Cl, 4·37% N; found: 56·30% C, 7·30% H, 21·97% Cl, 4·47% N.

5-(3-Dimethylaminopropyl)-8-chloro-2,3-dihydro-1-benzoxepin (*XXVI*)

A mixture of 10·0 g alcohol *XXXIII* and 150 ml 3N-H_2SO_4 was refluxed for 3 h in a 150°C oil bath. After cooling, the solution was washed with ether, made alkaline with a solution of sodium hydroxide and extracted with ether. Drying and evaporation of the extract and distillation of the residue yielded 8·65 g (93%) crude product boiling at 140—153°C/0·9 Torr. Check of the sample by chromatography on a thin layer of alumina showed the substance to be a mixture of two components with close R_F values. Picrate was prepared in the usual way from the base and crystallized from a mixture of ethanol and acetone. The predominating component of the mixture crystallized first and was readily obtained in a pure state: 14·15 g (88%), m.p. 99—100°C (ethanol). For $C_{21}H_{23}ClN_4O_8$ (494·9) calculated: 50·97% C, 4·68% H, 7·16% Cl, 11·32% N; found: 51·16% C, 4·76% H, 7·35% Cl, 10·95% N.

Decomposition of this picrate by alkalinization and extraction with ether yielded a base boiling at 154°C/0·4 Torr. On the basis of its UV spectrum the compound is assumed to have structure *XXVI*. λ_{max} 214 nm (log ε 4·303), 251 nm (4·064), 286 nm (3·347). IR spectrum (substance): 829 and 878 (1,2,4-trisubstituted benzene), 1 043 and 1 220 (Ar—O—R), 1 592 (Ar), 1 643 (conjugated C=C), 2 730 and 2 770 cm^{-1} (N—CH_3). For $C_{15}H_{20}ClNO$ (265·8) calculated: 67·78% C, 7·58% H, 13·34% Cl, 5·27% N; found: 67·42% C, 7·59% H, 13·26% Cl, 5·21% N.

Hydrochloride, m.p. 176—177°C (acetone–ether). For $C_{15}H_{21}Cl_2NO$ (302·3) calculated: 59·61% C, 7·00% H, 23·46% Cl, 4·63% N; found: 59·47% C, 7·12% H, 23·57% Cl, 4·82% N.

Hydrogen maleate, m.p. 86·5—88°C (acetone–ether). For $C_{19}H_{24}ClNO_5$ (381·9) calculated: 59·76% C, 6·33% H, 9·29% Cl, 3·67% N; found: 59·84% C, 6·30% H, 9·31% Cl, 3·69% N.

5-(3-Dimethylaminopropylidene)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXXVII*)

The last mother liquors after crystallization of the picrate of the preceding base gave rise to a small amount of precipitate of the isomeric light-yellow picrate melting at 143—146°C (ethanol). For $C_{21}H_{23}ClN_4O_8$ (494·9) calculated: 50·97% C, 4·68% H, 7·16% Cl, 11·32% N; found: 51·06% C, 4·66% H, 7·20% Cl, 11·22% N. Decomposition of this picrate yielded an oily base, the UV spectrum of which, compared with that of the base *XXVI* (see also ref.[13,23]) suggests structure *XXXVII*: λ_{max} 239 nm (log ε 4·010), 283 nm (3·390). IR spectrum: 812, 864 (1,2,4-trisubstituted benzene), 1 045, 1 218 and 1 232 (Ar—O—R), 1 593 cm^{-1} (Ar).

5-(3-Dimethylaminopropyl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXIV*)

A mixture of 6·6 g alcohol *XXXIII*, 26·6 ml acetic acid, 26·6 ml 56% hydroiodic acid and 3·2 g red phosphorus was refluxed under stirring for 4 h in a nitrogen atmosphere, in a bath heated to 130—135°C. The mixture was filtered while hot, the filtrate was evaporated at reduced pressure, the residue made alkaline with 20% sodium hydroxide and extracted with benzene. Treatment of the extract yielded 2·3 g (37%) base boiling at 140—150°C/1·2 Torr.

Hydrochloride, m.p. 190°C (acetone). For $C_{15}H_{23}Cl_2NO$ (304·3) calculated: 59·21% C, 7·62% H, 23·31% Cl, 4·60% N; found: 58·93% C, 7·67% H, 23·25% Cl, 4·61% N.

Hydrogen maleate, m.p. 115—116°C (acetone–ether). For $C_{19}H_{26}ClNO_5$ (383·9) calculated: 59·45% C, 6·83% H, 9·23% Cl, 3·65% N; found: 59·45% C, 7·04% H, 9·44% Cl, 3·63% N.

5-(3-Methylaminopropyl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XXXV*)

A solution of 9·6 g alcohol *XXXIII* in 70ml benzene was added dropwise to a boiling solution of 12·0 g ethyl chloroformate in 30 ml benzene and the mixture was refluxed for 7 h. After cooling, the precipitated crystals were filtered (4·0 g, m.p. 201—202°C) and identified as the hydrochloride of the starting amino alcohol *XXXIII*. The filtrate was washed with 10% sulfuric acid and water, the benzene solution was dried with potassium carbonate and evaporated at reduced pressure. The obtained oily neutral product (6·0 g, 55%) is not quite homogeneous and represents for the most part hydroxycarbamate *XXXIV*. The total amount of this product was dissolved in 6·5 ml ethanol and, after adding 3·2 g sodium hydroxide, it was refluxed for 2·5 h in a 120—125°C bath. After cooling, it was diluted with water and extracted with benzene. The basic fractions of the benzene extract were extracted into 15% hydrochloric acid. Evaporation of the washed benzene solution recovered 3·6 g of a neutral substance. The acid aqueous solution was made alkaline and extracted with ether. Evaporation of the extract yielded 1·95 g of a mixture of bases which crystallized on standing to 0·35 g compound melting at 121—123°C (benzene–light petroleum). According to analysis and spectra, the compound in question is 5-(3-*methylaminopropyl*)-8-*chloro*-2,3-*dihydro*-1-*benzoxepin* (XXVII). UV spectrum: λ_{max} 223·5 nm (log ε 4·469), 246 nm (4·187), 285 nm (3·724). IR spectrum: 809 and 885 (1,2,4-trisubstituted benzene), 1 237, 1 269 and 1 280 (Ar—O—R), 1 625 cm^{-1} (Ar). For $C_{14}H_{18}ClNO$ (251·8) calculated: 66·79% C, 7·20% H, 14·08% Cl, 5·56% N; found: 66·64% C, 7·36% H, 13·80% Cl, 5·47% N.

The fraction obtained after filtration of the crystalline compound *XXVII* was converted by treatment with anhydrous hydrogen chloride in an ether solution to a *hydrochloride* of *XXXV*, melting at 179—181°C (ethanol–acetone–ether). UV spectrum: λ_{max} 218 nm (log ε 4·030), IR spectrum: 812—909 (1,2,4-trisubstituted benzene), 1 033 and 3 366 (OH), 1 212 (Ar—O—R), 1 567 and 1 596 (Ar), 2 450 cm^{-1} (N···HCl). For $C_{14}H_{21}Cl_2NO_2$ (306·2) calculated: 54·91% C, 6·91% H, 23·16% Cl, 4·57% N; found: 55·16% C, 7·03% H, 22·94% Cl, 4·59% N.

5-Phenyl-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XXXVI*)

A solution of 14·7 g ketone *I* in 60 ml ether was added dropwise to a solution of phenylmagnesium bromide (from 17·7 g bromobenzene and 2·7 g magnesium in 40 ml ether) and the mixture was refluxed for 4·5 h. After cooling, it was decomposed with a saturated solution of ammonium chloride, the ether layer was dried with magnesium sulfate and evaporated. Upon standing, the oily residue (19·7 g) crystallized to the product: 9·7 g (47%), m.p. 144·5—145·5°C (ethanol). UV spectrum: λ_{max} 214·5 nm (log ε 4·230), 270 nm (3·248), 278 nm (3·249). IR spectrum: 704 and 771 (monosubstituted benzene), 820—879 (1,2,4-trisubstituted benzene), 1 037 and 3 435 (OH), 1211 (Ar—O—R), 1 571 and 1 596 cm^{-1} (Ar). For $C_{16}H_{15}ClO_2$ (274·8) calculated: 69·95% C, 5·50% H, 12·90% Cl; found: 70·18% C, 5·43% H, 12·90% Cl.

5-Phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XXVIII*)

Similarly to the preceding case, 9·8 g ketone *I* reacted with phenylmagnesium bromide and the crude product obtained was distilled *in vacuo*. 5·4 g (42%) of a fraction boiling between 160 and 180°C/1 Torr was obtained which was redistilled to an analytical product boiling at 160—164°C at 0·4 Torr. UV spectrum: λ_{max} 231 nm (log ε 4·262), 260 nm (4·076). IR spectrum (substance): 704 and 768 (monosubstituted benzene), 828—880 (1,2,4-trisubstituted benzene), 1 230 (Ar—O—R), 1 584 cm^{-1} (Ar). For $C_{16}H_{13}ClO$ (256·7) calculated: 74·85% C, 5·10% H, 13·81% Cl; found: 74·79% C, 5·28% H, 13·87% Cl.

5-Phenyl-5-(2-dimethylaminoethoxy)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XXXVIII*)

Similarly to the preparation of ether *XIII*, 9·0 g alcohol *XXXVI*, 2·3 g sodium amide and 4·2 g 2-dimethylaminoethyl chloride were treated in 50 ml benzene. The obtained crude base was converted directly to the *hydrochloride*; 4·55 g (36%), m.p. 168—170°C (acetone). UV spectrum: λ_{max} 278 nm (log ε 3·260). IR spectrum 710 and 769 (monosubstituted benzene), 829—899 (1,2,4-trisubstituted benzene), 1 068, 1 110 and 1 210 (Ar—O—R, R—O—R'), 1 599 cm^{-1} (Ar). For $C_{20}H_{25}Cl_2NO_2$ (382·3) calculated: 62·83% C, 6·59% H, 18·55% Cl, 3·66% N; found: 62·77% C, 6·96% H, 18·35% Cl, 3·51% N.

4-(Piperidinomethyl)-8-chloro-2,3-dihydro-4*H*-1-benzoxepin-5-one (*XXXIX*)

28 g paraformaldehyde was added under stirring over a period of 3 h to a boiling mixture of 68·6 g ketone *I*, 42 g piperidine hydrochloride, 210 ml ethanol and 3·5 ml concentrated hydrochloric acid. The mixture was then refluxed for 12 h. Ethanol was evaporated at reduced pressure, the residue was dissolved in 250 ml water and the solution was washed with ether. Evaporation. of the ether yielded 13·5 g neutral fraction from which a small amount of substance melting at 185—187°C (ethanol) crystallized on standing. According to analysis, spectra and analogy (see ref.[14]) the compound has the dimer structure *XLIII*. UV spectrum (saturated solution): λ_{max} 218, 260, 275 and 296 nm. IR spectrum 836—906 (1,2,4-trisubstituted benzene), 1 088 and 1 215 (ethers), 1 559 and 1 594 (Ar), 1 652 (C=C), 1 700 cm^{-1} (conjugated CO). For $C_{22}H_{18}Cl_2O_4$ (417·3) calculated: 63·32% C, 4·34% H, 16·99% Cl; found: 63·33% C, 4·48% H, 16·89% Cl.

The original acid aqueous solution was made alkaline with a solution of sodium hydroxide and the base *XXXIX* was isolated by extraction with ether; 82·3 g (80%) crude product. The *hydrochloride* was prepared with the aid of an ether solution of hydrogen chloride; m.p. 220°C with decomposition (changes starting at 173°C). For $C_{16}H_{21}Cl_2NO_2$ (330·3) calculated: 58·19% C, 6·41% H, 21·47% Cl, 4·24% N; found: 57·94% C, 6·50% H, 21·49% Cl, 4·50% N.

Hydrogen maleate, m.p. 127—128°C and after solidification 164—166°C (ethanol). For $C_{20}.H_{24}ClNO_6$ (409·9) calculated: 58·61% C, 5·90% H, 8·65% Cl, 3·42% N; found: 58·81% C, 5·83% H, 8·86% Cl, 3·54% N.

A similar course was recorded in the case of reaction of ketone *I* and piperidine with aqueous formaldehyde in ethanol but the yield of the Mannich base *XXXIX* was lower.

4-Piperidinomethyl-5-acetoxy-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XLI*)

A solution of 16·2 g sodium borohydride in 50 ml water with a small amount of sodium hydroxide was added dropwise to a solution of 28·5 g crude base *XXXIX* in 430 ml methanol. The mixture was refluxed for 2·5 h; after cooling, methanol was evaporated at reduced pressure, the residue was diluted with water and extracted with benzene. Evaporation of the extract yielded 28·6 g crude mixture of racemic alcohols *XL* which could not be induced to crystallization. Therefore, the entire amount was mixed with acetic anhydride and refluxed for 4 h at 160°C. After partial cooling, 100 ml water was added and excess acetic anhydride was decomposed by heating. The mixture was then evaporated *in vacuo*, the residue was carefully made alkaline with dilute sodium hydroxide and the liberated base was immediately isolated by extraction with ether. Distillation yielded 18·2 g of a fraction boiling at 160—173°C/0·4 Torr from which an ether solution of hydrogen chloride gave 4·9 g *hydrochloride of the amino ester* XLI; m.p. 188—191°C (acetone–ether). UV spectrum: λ_{max} 220 nm (log ε 4·251), 267 nm (3·791), 275 nm (3·783), 310 nm (3·399). IR spectrum: 814—892 (1,2,4-trisubstituted benzene), 1 048, 1 283 (ether), 1 597 (Ar), 1 730 (RCOOR'), 2 420 and 2 483 cm^{-1} (N···HCl). For $C_{18}H_{25}Cl_2NO_3$ (374·3) calculated: 57·76% C, 6·73% H, 18·95% Cl, 3·74% N; found: 58·27% C, 6·69% H, 19·38% Cl, 3·93% N.

Treatment of the mother liquor after the preceding hydrochloride yielded 1·0 g of another compound, melting at 209—211°C (ethanol–ether) which, according to analysis and spectra, is a *hydrochloride of the amino alcohol* XL. UV spectrum: λ_{max} 217·5 nm (log ε 3·962). IR spectrum: 821—892 (1,2,4-trisubstituted benzene), 1046 and 1220 (ether), 1572 and 1596 (Ar), 2550, 2670 and 2687 (N···HCl), 3226 cm^{-1} (OH). For $C_{16}H_{23}Cl_2NO_2$ (332·3) calculated: 57·83% C, 6·98% H, 21·34% Cl, 4·22% N; found: 57·92% C, 6·99% H, 21·27% Cl, 4·37% N.

4-Piperidinomethyl-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XLII*)

A solution of 22 g Mannich base *XXXIX* in 40 ml ether was added dropwise under gentle refluxing to a solution of phenylmagnesium bromide (prepared from 17·7 g bromobenzene and 2·7 g magnesium in 40 ml ether and 10 ml tetrahydrofuran). The mixture was refluxed for further 4 h, cooled, decomposed by pouring into a solution of ammonium chloride and extracted with a mixture of benzene and chloroform. The product obtained by evaporation of the extract partly crystallized after dissolving in a warm mixture of 20 ml cyclohexane and 60 ml light petroleum: 11·3 g (41%), m.p. 159—160°C. UV spectrum: λ_{max} 214·5 nm (log ε 4·269), 219 nm (4·234), 226 nm (4·090), 249·5 nm (3·507), 279 nm (3·382). IR spectrum: 700 and 755 (monosubstituted benzene), 837 and 889 (1,2,4-trisubstituted benzene), 1043 and 3200 (OH), 1299 (Ar—O—R), 1589 cm^{-1} (Ar). For $C_{22}H_{26}ClNO_2$ (371·9) calculated: 71·05% C, 7·05% H, 9·53% Cl, 3·77% N; found: 71·35% C, 7·12% H, 9·64% Cl, 4·00% N.

Hydrochloride, m.p. 249—252°C (ethanol–acetone–ether). For $C_{22}H_{27}Cl_2NO_2$ (408·4) calculated: 64·70% C, 6·66% H, 17·37% Cl, 3·43% N; found: 64·61% C, 6·57% H, 17·25% Cl, 3·20% N.

4-Piperidinomethyl-5-phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XLIV*)

A mixture of 5·0 g alcohol *XLII*, 20 ml ethanol and 10 ml concentrated hydrochloric acid was refluxed for 1 h. Then it was evaporated to dryness *in vacuo*, the residue treated with a solution of sodium hydroxide to release the base and the base was extracted with benzene. Drying and evaporation of the extract produced an almost theoretical yield (4·7 g) of the product: m.p. 124°C (ethanol). UV spectrum: λ_{max} 217 nm (log ε 4·398), 232·5 nm (4·267), 256·5 nm (4·217). IR spectrum: 698 and 754 (monosubstituted benzene), 812—874 (1,2,4-trisubstituted benzene), 1299 (Ar—O—R), 1556 and 1590 cm^{-1} (Ar). For $C_{22}H_{24}ClNO$ (553·9) calculated: 74·66% C, 6·84% H, 10·02% Cl, 3·96% N; found: 74·74% C, 6·94% H, 9·93% Cl, 3·98% N.

Hydrochloride, m.p. 193—194°C (acetone–ether). For $C_{22}H_{25}Cl_2NO$ (390·4) calculated: 67·69% C, 6·45% H, 18·17% Cl, 3·59% N; found: 67·52% C, 6·52% H, 17·90% Cl, 3·74% N.

The detailed pharmacological tests for neurotropic activity were carried out by Dr J. Metyšová and Dr J. Metyš of the pharmacological department of this Institute. Detailed analyses of cardiovascular activity of some selected compounds were done by Dr F. Trčka, compound XX *was tested in cooperation with Dr A. Dlabač. The antiinflammatory effects were tested under the direction of Dr J. Grimová of the pharmacological department. Pharmacological screening of most compounds was done by Dr J. Němec at the unit of this institute at Rosice n/L. Antimicrobial activity was evaluated by Dr J. Turinová at the bacteriological department (head Dr A. Šimek). The NMR spectrum of compound* XXIX (*ZKR 60 Zeiss, Jena*) *was recorded and interpreted by Dr B. Kakáč at the department of physical chemistry of this Institute. The mass spectrometry was performed by Dr V. Hanuš, Institute of Physical Chemistry, Czechoslovak Academy of Sciences, Prague. The analytical estimations were done at the analytical department (head Dr J. Körbl) by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs A. Slavíková. Mrs M. Hrubantová assisted with the preparation of the compounds.*

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